

PYRROLIDINE-2-ONES AS FACTOR XA INHIBITORS

Field of the Invention

5 The present invention relates to a novel class of chemical compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.

10

Background of the Invention

Factor Xa is a member of the trypsin-like serine protease class of enzymes. It is a key enzyme in the coagulation cascade. A one-to-one binding of Factors Xa and Va with calcium ions and phospholipid converts prothrombin into thrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. The insoluble fibrin matrix is required for the stabilisation of the primary hemostatic plug. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Both treatment of an occlusive coronary thrombus by thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) are often accompanied by an acute thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterised by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure. Beyond its direct role in the formation of fibrin rich blood clots, thrombin has been reported to have profound bioregulatory effects on a number of cellular components within the vasculature and blood, (Shuman, M.A., Ann. NY Acad. Sci., 405: 349 (1986)).

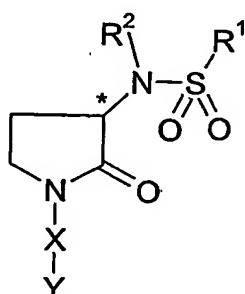
35

A Factor Xa inhibitor may be useful in the treatment of acute vascular diseases such as acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequelae associated with myocardial infarction or heart failure), thromboembolism, acute vessel closure associated

with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke. Factor Xa inhibitors 5 may also be useful in preventing thrombosis and complications in patients genetically predisposed to arterial thrombosis or venous thrombosis and patients that have a disease-associated predisposition to thrombosis (e.g. type 2 diabetics). Thrombin has been reported to contribute to lung fibroblast proliferation, thus, Factor Xa inhibitors could be useful for the treatment of some pulmonary fibrotic diseases. Factor Xa inhibitors could 10 also be useful in the treatment of tumour metastasis, by suppressing coagulation and thus preventing fibrin deposition and its concommittant facilitation of metastasis. A Factor Xa inhibitor may also have utility as an anti-inflammatory agent through its inhibition of FXa mediated activation of protease-activated receptors (PARs 1 and 2). A Factor Xa inhibitor may also have utility as an anti-atherosclerotic agent through the suppression of platelet- 15 activation. Thrombin can induce neurite retraction and thus Factor Xa inhibitors may have potential in neurodegenerative diseases such as Parkinson's and Alzheimer's disease. Factor Xa inhibitors may also have utility as anticoagulant agents in connection with the preparation, storage, fractionation or use of whole blood. They have also been reported for use in conjunction with thrombolytic agents, thus permitting the use of a lower dose of 20 thrombolytic agent.

Description of the Invention

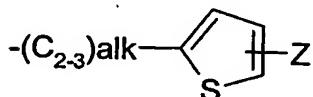
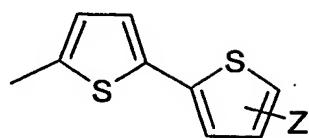
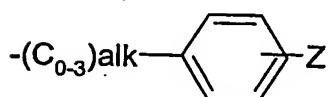
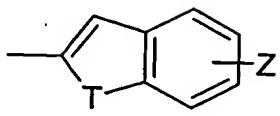
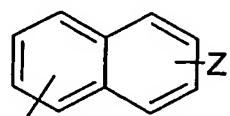
The present invention provides compounds of formula (I):



25

wherein:

R^1 represents a group selected from:



each ring of which optionally contains a further heteroatom N,

Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

5 T represents S, O or NH;

R^2 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{1-3}$ alkylCONR^aR^b, $-C_{1-3}$ alkylCO₂C₁₋₄alkyl, $-CO_2C_{1-4}$ alkyl or $-C_{1-3}$ alkylCO₂H;

10 R^a and R^b independently represent hydrogen, $-C_{1-6}$ alkyl, or together with the N atom to which they are bonded form a 5-, 6- or 7- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S, optionally substituted by $-C_{1-4}$ alkyl, and optionally the S heteroatom is substituted by O, i.e. represents S(O)_n;

15

n represents 0-2;

X represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-

20 2 groups selected from: halogen, $-C_{1-4}$ alkyl, $-C_{2-4}$ alkenyl, -CN, -CF₃, -NR^aR^b, $-C_{0-4}$ alkylOR^e, -C(O)R^f and -C(O)NR^aR^b;

R^e represents hydrogen or $-C_{1-6}$ alkyl;

R^f represents $-C_{1-6}$ alkyl;

Y represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is substituted by a group – C₁₋₂alkylNR^cR^d.

5 R^c and R^d, together with the nitrogen atom to which they are bonded, form a 4-membered heterocyclic ring optionally substituted by halogen, OH or –OC₁₋₆alkyl, or a 5- or 6-membered non-aromatic heterocyclic ring substituted by OH, –OC₁₋₆alkyl or 1 to 2 halogens, with the proviso that the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

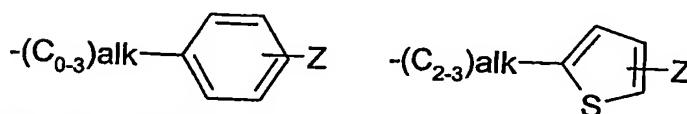
10 and/or pharmaceutically acceptable derivative thereof.

Further aspects of the invention are:

- A pharmaceutical composition comprising a compound of the invention together with a pharmaceutical carrier and/or excipient.
- A compound of the invention for use in therapy.
- Use of a compound of the invention for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

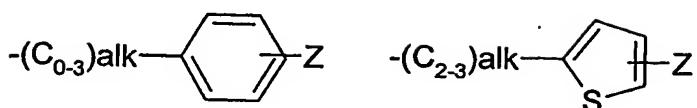
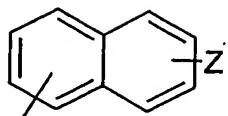
20 - A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of a compound of the invention.

In one aspect of the invention, R¹ represents a group selected from:



25 each ring of which optionally contains a further heteroatom N,
 Z represents an optional substituent halogen,
 alk represents alkylene or alkenylene,
 T represents S, O or NH.

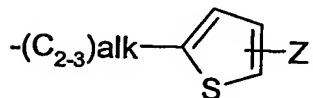
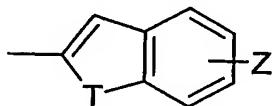
30 In one aspect of the invention, R¹ represents a group selected from:



each ring of which optionally contains a further heteroatom N,
 Z represents an optional substituent halogen,
 alk represents alkylene or alkenylene.

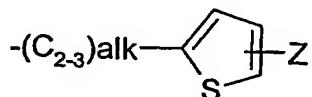
5

In another aspect, R¹ represents a group selected from:



10 Z represents an optional substituent halogen,
 alk represents alkylene or alkenylene,
 T represents S, O or NH.

In another aspect, R¹ represents a group selected from:
 15



Z represents an optional substituent halogen,

alk represents alkylene or alkenylene.

In one aspect of the invention, T represents a S atom.

5 In one aspect of the invention, R² represents hydrogen.

In one aspect of the invention, R^a and R^b independently represent hydrogen or -C₁₋₆alkyl.

In one aspect of the invention, X represents phenyl or a 5 or 6 membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, -C₁₋₄alkyl or -NR^aR^b.
10 In another aspect, X represents phenyl substituted by a halogen. In another aspect, X represents phenyl substituted by a fluorine.

15 In one aspect of the invention, Y represents a 5 or 6 membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is substituted by a group -CH₂NR^cR^d.

20 In another aspect, Y represents a 5 membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, substituted by a group -CH₂NR^cR^d.

In another aspect, Y represents imidazole substituted by a group -CH₂NR^cR^d.

25 In one aspect of the invention, R^c and R^d, together with the nitrogen atom to which they are bonded, form an azetidine optionally substituted by halogen, OH or -OC₁₋₆alkyl, or a pyrrolidine ring with a substituent selected from halogen, OH or -OC₁₋₆alkyl.

30 In another aspect of the invention, R^c and R^d, together with the nitrogen atom to which they are bonded, form an azetidine optionally substituted by halogen or -OC₁₋₆alkyl, or a pyrrolidine ring with a substituent selected from halogen.

In another aspect, R^c and R^d, together with the nitrogen atom to which they are bonded, form an azetidine ring optionally substituted by halogen, or a pyrrolidine ring with a substituent selected from halogen.

35

In another aspect of the invention, R^c and R^d, together with the nitrogen atom to which they are bonded, form an azetidine optionally substituted by -OC₁₋₆alkyl, or a pyrrolidine ring with a substituent selected from halogen.

In another aspect, R^c and R^d , together with the nitrogen atom to which they are bonded, form an azetidine ring optionally substituted by $-OCH_3$ or a pyrrolidine ring with a substituent fluorine.

5

It is to be understood that the present invention covers all combinations of the various aspects of the invention described herein above.

The compounds of formula (I) contain chiral (asymmetric) centres. The individual 10 stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention. In one aspect of the invention, the stereochemistry is (S) at the 3-position on the 2-oxopyrrolidine ring (*).

As used herein, the term "alkyl" means both straight and branched chain saturated 15 hydrocarbon groups. Examples of alkyl groups include methyl ($-CH_3$), ethyl ($-C_2H_5$), propyl ($-C_3H_7$) and butyl ($-C_4H_9$).

As used herein, the term "alkylene" means both straight and branched chain saturated hydrocarbon linker groups. Examples of alkylene groups include methylene ($-CH_2-$), 20 ethylene ($-CH_2CH_2-$) and propylene ($-CH_2CH_2CH_2-$).

As used herein, the term "alkenylene" means both straight and branched chain unsaturated hydrocarbon linker groups, wherein the unsaturation is present only as double bonds. Examples of alkenylene groups includes ethenylene ($-CH=CH-$) and 25 propenylene ($-CH_2-CH=CH-$).

As used herein, the term "heterocyclic group" means optionally substituted rings containing one or more heteroatoms selected from: nitrogen, sulphur and oxygen atoms. The heterocycle may be aromatic or non-aromatic, i.e., may be saturated, partially or fully 30 unsaturated. Examples of 5-membered groups include thienyl, furanyl, pyrrolidinyl thiazolyl, oxazolyl and imidazolyl. Examples of 6-membered groups include pyridyl, piperidinyl, pyrimidinyl and morpholinyl. Examples of 7- membered groups include hexamethyleneiminy. Certain heterocyclic groups, e.g. thienyl, furanyl, thiazolyl, oxazolyl, 35 pyridyl and pyrimidinyl are C-linked to the rest of the molecule. Other heterocyclic groups, e.g pyrrolidinyl, imidazolyl, piperidyl, morpholinyl and hexamethyleneiminy may be C-linked or N-linked to the rest of the molecule.

As used herein, the term "halogen" means an atom selected from fluorine, chlorine, bromine and iodine.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

5 As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), or an active metabolite or residue thereof. Preferred pharmaceutically acceptable derivatives 10 are salts, solvates, esters and carbamates. Particularly preferred pharmaceutically acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and solvates.

Suitable salts according to the invention include those formed with both organic and 15 inorganic acids and bases. Pharmaceutically acceptable acid addition salts include those formed from mineral acids such as: hydrochloric, hydrobromic, sulphuric, phosphoric, acid; and organic acids such as: citric, tartaric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, formic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, 20 p-toluenesulphonic, benzenesulphonic and isethionic acids. Particularly preferred pharmaceutically acceptable salts include those formed from hydrochloric, trifluoroacetic and formic acids.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are 25 precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I) are within the scope of the invention.

30 Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts and solvates.

35 As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche,

ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", *Advanced Drug Delivery Reviews* (1996) 19(2) 115-130, each of which are incorporated herein by reference.

5

Prodrugs are any covalently bonded carriers that release a compound of structure (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for 10 example, compounds of this invention wherein hydroxyl or amine groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxyl or amine groups.

Esters may be active in their own right and/or be hydrolysable under *in vivo* conditions in 15 the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. An ester may be formed at a carboxylic acid (-COOH) group or a hydroxyl (-OH) group, by methods well known in the art involving reaction with the corresponding alcohol, acid, acid chloride, anhydride, or amide. Preferred esters are C₁-6alkyl esters, e.g. methyl 20 esters, ethyl esters, and the like.

Preferred compounds of the invention include:

(1*E*)-*N*-(1-{4-[2-(1-Azetidinylmethyl)-1*H*-imidazol-1-yl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-2-(5-chloro-2-thienyl)-1-propene-1-sulfonamide;

25 *N*-(1-{4-[2-(1-Azetidinylmethyl)-1*H*-imidazol-1-yl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-2-(5-chloro-2-thienyl)ethanesulfonamide;

N-(3*S*)-1-{4-[2-(1-Azetidinylmethyl)-1*H*-imidazol-1-yl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-6-chloro-1-benzothiophene-2-sulfonamide.

(*E*)-2-(5-Chloro-2-thienyl)-*N*-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1*H*-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]ethenesulfonamide;

30 (1*E*)-2-(5-Chloro-2-thienyl)-*N*-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1*H*-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]ethenesulfonamide;

(1*E*)-2-(5-Chloro-2-thienyl)-*N*-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1*H*-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]-1-propene-1-sulfonamide;

35 6-Chloro-*N*-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1*H*-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]-1-benzothiophene-2-sulfonamide; and

6-Chloro-*N*-[1-(2-fluoro-4-{2-[(3-methyloxy)-1-azetidinyl]methyl}-1*H*-imidazol-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]-1-benzothiophene-2-sulfonamide formate.

Compounds of the invention may show advantageous properties, they may be more efficacious, may show greater selectivity, may have fewer side effects, may have a longer

duration of action, may be more bioavailable by the preferred route, or may have other more desirable properties than similar known compounds.

The compounds of formula (I) are Factor Xa inhibitors and as such are useful in the treatment of clinical conditions susceptible to amelioration by administration of a Factor Xa inhibitor. Such conditions include acute vascular diseases such as acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequelae associated with myocardial infarction or heart failure), thromboembolism, acute vessel closure associated with 5 thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke; in preventing thrombosis and complications in patients genetically predisposed to arterial thrombosis or 10 venous thrombosis and patients that have a disease-associated predisposition to thrombosis (e.g. type 2 diabetics); the treatment of pulmonary fibrosis; the treatment of tumour metastasis; inflammation; atherosclerosis; neurogenerative disease such as Parkinson's and Alzheimer's diseases; Kasabach Merritt Syndrome; Haemolytic uremic syndrome; endothelial dysfunction; as anti-coagulants for extracorporeal blood in for 15 example, dialysis, blood filtration, bypass, and blood product storage; and in the coating of invasive devices such as prostheses, artificial valves and catheters in reducing the risk of thrombus formation.

Accordingly, one aspect of the present invention provides a compound of formula (I) and/or a pharmaceutically acceptable derivative thereof for use in medical therapy, particularly 25 for use in the amelioration of a clinical condition in a mammal, including a human, for which a Factor Xa inhibitor is indicated.

In another aspect, the invention provides a method for the treatment and/or prophylaxis of 30 a mammal, including a human, suffering from a condition susceptible to amelioration by a Factor Xa inhibitor which method comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

In another aspect, the present invention provides the use of a compound of formula (I) and/or a pharmaceutically acceptable derivative thereof, for the manufacture of a 35 medicament for the treatment and/or prophylaxis of a condition susceptible to amelioration by a Factor Xa inhibitor.

In one aspect of the invention, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from treatment of acute vascular diseases such as acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequelae associated with myocardial

5 infarction or heart failure), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

10

In another aspect, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequelae associated with myocardial infarction or heart failure), pulmonary embolism, deep vein 15 thrombosis and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

20

While it is possible that, for use in therapy, a compound of the present invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

25 In a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

30

Accordingly, the present invention further provides a pharmaceutical formulation comprising at least one compound of formula (I) and/or a pharmaceutically acceptable derivative thereof, in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (I) and/or a pharmaceutically

acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

- 5 There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I) and/or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier and/or excipient.
- 10 The compounds for use according to the present invention may be formulated for oral, buccal, parenteral, topical, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions or they may be presented as a dry product for constitution with water or other suitable vehicles before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

30 Preparations for oral administration may be suitably formulated to give controlled/extended release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges 35 formulated in a conventional manner.

The compounds according to the present invention may be formulated for parenteral administration by injection, e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose

containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. 5 sterile pyrogen-free water, before use.

The compounds according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator.

10

Powders for external application may be formed with the aid of any suitable powder base, for example, lactose, talc or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

15

The compounds according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

20 In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for 25 example as an emulsion in an acceptable oil) or ion exchange resins or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, such as 1mg to 500mg of 30 the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The dosage will also depend on the route of 35 administration. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of formula (I) may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a

compound of formula (I) and/or a pharmaceutically acceptable derivative thereof together with one or more further therapeutic agent(s).

When a compound of formula (I) and/or a pharmaceutically acceptable derivative thereof

- 5 is used in combination with a second therapeutic agent the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately
- 10 at the discretion of the attendant physician or veterinarian. The compounds of the present invention may be used in combination with other antithrombotic drugs (such as thrombin inhibitors, thromboxane receptor antagonists, prostacyclin mimetics, phosphodiesterase inhibitors, fibrinogen antagonists, thrombolytic drugs such as tissue plasminogen activator and streptokinase, non-steroidal anti-inflammatory drugs such as aspirin, and the like),
- 15 anti-hypertensive agents (such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, ACE / NEP inhibitors, β -blockers, calcium channel blockers, PDE inhibitors, aldosterone blockers), anti-atherosclerotic / dyslipidaemic agents (such as HMG-CoA reductase inhibitors) and anti-arrhythmic agents.

20 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with at least one pharmaceutically acceptable carrier and/or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or

- 25 simultaneously in separate or combined pharmaceutical formulations by any convenient route.

When administration is sequential, either the Factor Xa inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination

- 30 may be administered either in the same or different pharmaceutical composition.

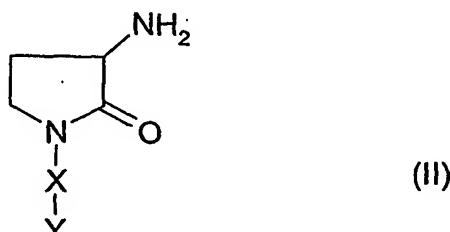
When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient

- 35 formulation, conveniently in such manner as are known for such compounds in the art.

The compounds of formula (I) and/or pharmaceutically acceptable derivatives thereof may be prepared by the processes described hereinafter, said processes constituting a further

aspect of the invention. In the following description, the groups are as defined above for compounds of formula (I) unless otherwise stated.

According to a further aspect of the present invention, there is provided a process (A) for 5 preparing a compound of formula (I) which comprises of reacting a compound of formula (II) or an acid addition salt thereof with a compound of formula (III) where V is a suitable leaving group, such as a halide, e.g. chloride. When the free base of a compound of formula (II) is used, the reaction is conveniently carried out in the presence of a base, e.g. pyridine, and in a suitable solvent, e.g. acetonitrile (MeCN), suitably at 0°C to room 10 temperature. When the acid addition salt of a compound of formula (II) is used, the reaction is conveniently carried out in the presence of a base, e.g. N,N-diisopropylethylamine (DIPEA), and in a suitable solvent, e.g. MeCN, suitably at 0°C to room temperature.

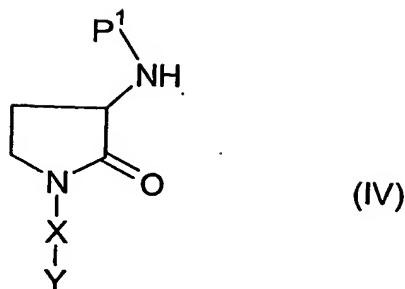


15

If X-Y contains a group reactive to compounds of formula (III), such groups may be protected prior to reaction of a compound of formula (II) with a compound of formula (III) using methods well known in the art and such protecting groups removed under standard conditions to provide compounds of formula (I) after completion of the reaction of a 20 compound of formula (II) with a compound of formula (III).

Compounds of formula (III) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

25 Compounds of formula (II) may be prepared from compounds of formula (IV):

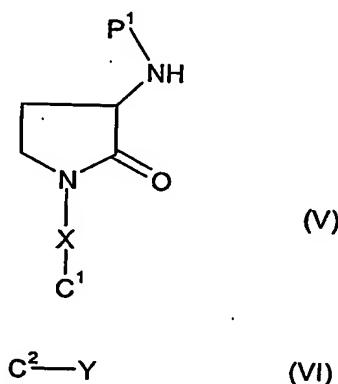


wherein P¹ is a suitable amine protecting group, e.g. Boc (t-butyloxycarbonyl), by removal of the protecting group under standard conditions. For example, when P¹ represents Boc, removal of the protecting group may be effected under acidic conditions, using for example TFA (trifluoroacetic acid) in a solvent such as dichloromethane (DCM) suitably at room temperature.

5

Compounds of formula (IV) may be prepared by metal-catalysed coupling of a compound of formula (V) with a compound of formula (VI):

10



15 where C¹ and C² are suitable coupling groups, e.g. when bonded to a ring carbon atom C¹ and C² can be boronate [B(OH)₂], halide e.g. iodide (I), trifluoromethanesulfonate (OTf) or stannane such as trialkyltin, and P¹ is as defined above. C² can also be hydrogen when directly bonded to a heteroatom of Y. A suitable metal catalyst includes palladium(0) or a salt thereof in the presence of a ligand, e.g., triphenylphosphine and a base, e.g., sodium 20 carbonate, and optionally with a suitable co-solvent, e.g. water, suitably at a temperature range from room temperature to 150 °C. For example, when C¹ is B(OH)₂ and C² is a bromide, coupling of compounds of formula (V) with compounds of formula (VI) can be effected with tetrakis(triphenylphosphine)palladium(0) in the presence of sodium carbonate in aqueous tetrahydrofuran at 70 to 80 °C.

25

It will be appreciated by persons skilled in the art that certain combinations of coupling groups C^1 and C^2 in compounds of formula (V) and (VI) and metal catalysts are preferred. Examples of these can be found in Smith, M.B. and March, J., Advanced Organic

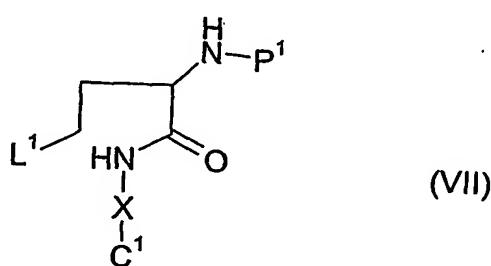
5 will also appreciated that coupling groups, C^1 and C^2 , in compounds of formula (V) and (VI) may be interconverted using known methods.

Alternatively, when C^2 is a hydrogen directly bonded to a heteroatom of Y, compounds of formula (IV) may be prepared by metal-catalysed coupling of a compound of formula (VI) 10 with a compound of formula (V) where C^1 is a suitable coupling group, such as halide e.g. iodide, P^1 is as defined above. Suitable metal catalysts include palladium(0) or a salt thereof in the presence of a suitable ligand, e.g. tri-o-tolylphosphine or a copper salt e.g. copper (I) iodide, in the presence of a suitable ligand, e.g. 8-hydroxyquinoline or N,N'-dimethylethylene-1,2-diamine, in the presence of a solvent, e.g. DMSO, and a base, e.g. 15 sodium *tert*-butoxide or potassium carbonate, and optionally with a suitable co-solvent, e.g. triethylamine, suitably at room temperature to 150 °C. For example, when C^1 is iodide, coupling of compounds of formula (V) with compounds of formula (VI) can be effected with copper (I) iodide and a ligand, e.g. 8-hydroxyquinoline or N,N'-dimethylethylene-1,2-diamine, in the presence of a base, e.g. potassium carbonate, in a 20 suitable solvent, e.g. dimethyl sulphoxide (DMSO), suitably at elevated temperature, such as 70-150°C, e.g. 100-130°C.

Compounds of formula (VI) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

25

Compounds of formula (V) may be prepared from compounds of formula (VII):

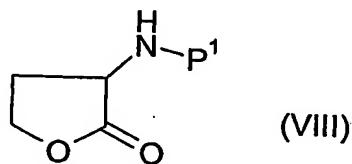


30 by cyclisation where C^1 represents a group as defined above and L^1 represents a suitable leaving group, e.g. hydroxyl. For example, when L^1 is a hydroxyl group, the ring closure may be performed under Mitsunobu conditions, e.g. by treatment with a mixture of (i) aryl or alkyl phosphine, e.g. tri-n-butylphosphine, and (ii) a suitable azodicarboxylate

derivative, e.g. 1,1'-(azodicarbonyl)-dipiperidine, in a suitable solvent, e.g. THF (tetrahydrofuran), suitably at 0°C to room temperature.

It will be appreciated by persons skilled in the art that compounds of formula (VII) may be 5 prepared by interconversion, utilising other compounds of formula (VII) which are optionally protected by standard protecting groups, as precursors. For instance, compounds of formula (VII) where L¹ is OH, may be converted into compounds of formula (VII) possessing alternative substituents at L¹, e.g. halogen, S⁺MeR W⁻ or OSO₂R, by methods well known in the art (see for example Smith, M.B. and March, J., Advanced 10 Organic Chemistry, 5th Edition 2001, John Wiley & Sons). Generally R will represent alkyl or aralkyl and W will represent sulphate or halide, especially iodide. In such cases the ring closure may be performed by treatment with a base in a suitable solvent, e.g. MeCN.

Compounds of formula (VII), where L¹ is a hydroxyl group, may be prepared by reacting a 15 compound of formula (VIII) with a compound of formula (IX):

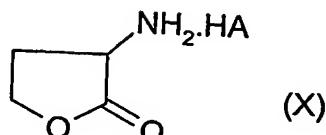


wherein P¹ is a suitable protecting group as described above. The reaction is conveniently carried out by addition of a suitable activating agent, e.g. trimethylaluminium, 20 to compounds of formula (IX) in a suitable solvent e.g. DCM, under an inert atmosphere, e.g. nitrogen, suitably at room temperature followed by addition of a compounds of formula (IX) in a compatible solvent e.g. DCM.

Compounds of formula (IX) are known compounds or may be prepared by methods 25 known in the literature or processes known to those skilled in the art.

Compounds of formula (VIII) may be prepared from compounds of formula (X) where HA is a suitable acid, e.g. hydrochloric acid, using methods well known to those skilled in the art. See, for example, "Protective groups in organic synthesis" by T.W. Greene and

P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994).



5

Compounds of formula (X) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

There is provided a further process (B) for preparing compounds of formula (I) where R^2 is

10 a substituent other than hydrogen, which comprises reacting a compound of formula (I) where R^2 is hydrogen with a compound of formula (XI):

15



where R^2 is $-C_{1-6}\text{alkyl}$, $-C_{1-3}\text{alkyl}CONR^aR^b$, $-C_{1-3}\text{alkyl}CO_2C_{1-4}\text{alkyl}$ or $-CO_2C_{1-4}\text{alkyl}$ and T is a suitable leaving group such as that derived from a hydroxyl group or halide, e.g. bromide, optionally followed by removal of the alkyl protecting group, e.g. t-Butyl, under standard conditions to form a compound wherein R^2 is $C_{1-3}\text{alkyl}CO_2H$. When T is halide, the reaction is effected in a suitable organic solvent, e.g. THF or DMF, in the presence of a base, e.g. LiHMDS (lithium hexamethyldisilylamide), potassium carbonate or sodium carbonate, at a temperature range from -78°C to $+50^\circ\text{C}$, such as -78°C to room temperature. When T is a hydroxyl group, the reaction is effected under Mitsunobu conditions (for examples see Hughes, David L. *Progress in the Mitsunobu reaction*. A review. *Organic Preparations and Procedures International* (1996), 28(2), 127-64.). For example, the reaction may be performed by treatment of compounds of formula (I) where R^2 represents H with an aryl or alkyl phosphine e.g., triphenylphosphine, optionally bound to polymer-support, and an azodicarboxylate derivative, e.g. di-*tert*-butyl azodicarboxylate, 20 in a suitable solvent, e.g., THF (tetrahydrofuran), followed by addition of a compound of formula (XI) where T represents OH, optionally in a suitable solvent, e.g. THF, suitably at room temperature.

25

30

When X-Y contains a group reactive to compounds of formula (XI), such groups may be 35 protected prior to the reaction using methods well known in the art and such protecting groups removed under standard conditions to provide compounds of formula (I) where R^2

is a substituent other than hydrogen after completion of the reaction of a compound of formula (I) where R² is hydrogen with a compound of formula (XI).

Compounds of formula (XI) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

Furthermore, it will be appreciated that the substituent R², other than hydrogen, may be introduced at various intermediate stages by methods well known to those skilled in the art.

10

It will be appreciated by those skilled in the art that compounds of formula (I) or a solvate thereof may be synthesized from appropriate intermediates via solid phase chemistry processes.

15

Those skilled in the art will appreciate that in the preparation of the compound of formula (I) and/or solvates thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for

20

example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g.

25

9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropylloxycarbonyl, cyclohexyloxycarbonyl) and alkyl or aralkyl type protecting groups (e.g. benzyl, trityl, chlorotriyl). Examples of suitable hydroxyl protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate. Examples of carboxylic acid

30

protecting groups may include for example aralkyl groups, e.g. benzyl, or alkyl groups, e.g. t-butyl.

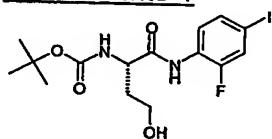
Various intermediate compounds used in the above-mentioned process, including but not limited to certain compounds of formulae (II), (IV) and (V) constitute a further aspect of the present invention.

The present invention will now be further illustrated by the accompanying examples which should not be construed as limiting the scope of the invention in any way.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

ExamplesAbbreviations

5	THF	Tetrahydrofuran
	DCM	Dichloromethane
	CBZ	carbobenzyloxy
	m	multiplet
	q	quartet
10	s	singlet
	t	triplet
	d	doublet
	dd	double doublet

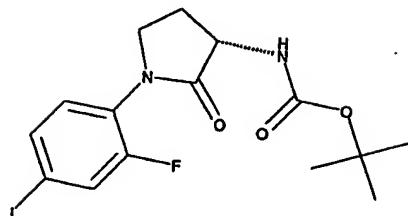
15 Intermediate 1

1,1-Dimethylethyl ((1S)-1-{[(2-fluoro-4-iodophenyl)amino]carbonyl}-3-hydroxypropyl)-carbamate

A solution of 2-fluoro-4-iodoaniline (7.11g) in anhydrous DCM (40ml) under N₂ at 0°C was treated dropwise with trimethylaluminium (2N in heptane; 15ml). The mixture was allowed to stir for 30min before a solution of 1,1-dimethylethyl [(3S)-2-oxotetrahydro-3-furanyl]carbamate (5.03g), in anhydrous DCM (35ml), was added dropwise. The reaction was allowed to warm up to ambient temperature and stirred for 18h, before quenching with 10% aqueous citric acid (10ml). Saturated aqueous potassium sodium tartrate (100ml) was then added with stirring followed by separation of the organic and aqueous layers. The organic layer was dried (over magnesium sulphate) and concentrated under reduced pressure. The residue was purified using Biotage™ chromatography (silica, eluting with cyclohexane:ethyl acetate 3:2) to afford an off-white solid which was an inseparable mixture (c. 1:2) of the starting material and the title compound (5.55g).

30 Mass spectrum: Found: M⁺ 439

Intermediate 2

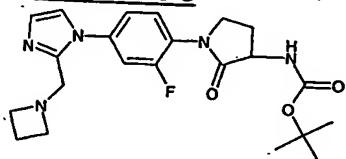


1,1-Dimethylethyl [(3S)-1-(2-fluoro-4-iodophenyl)-2-oxo-3-pyrrolidinyl]carbamate

To a solution of crude Intermediate 1 (5.55g) and tri-n-butylphosphine (3.49ml) in anhydrous THF (100ml) under N₂ at 0°C was added solid 1,1'-(azodicarbonyl)-dipiperidine (3.53g). The solution was allowed to warm to ambient temperature and stirred for 18h. The mixture was then diluted with cyclohexane (100ml) and the precipitate filtered off. The filtrate was then concentrated under reduced pressure and the residue purified using Biotage™ chromatography (silica, eluting with cyclohexane:ethyl acetate 2:1) to give the **title compound** (2.93g) as a white solid.

10 Mass spectrum: Found: M⁺ 421

Intermediate 3

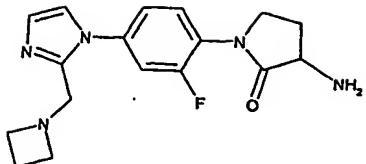


1,1-Dimethylethyl (1-[4-[2-(1-azetidinylmethyl)-1H-imidazol-1-yl]-2-fluorophenyl]-2-oxo-3-pyrrolidinyl)carbamate

A suspension of Intermediate 2 (2g), Intermediate 5 (0.713g) anhydrous potassium carbonate (0.704g), 8-hydroxyquinoline (0.044g) in anhydrous dimethylsulphoxide (4.8ml) was stirred under nitrogen at ambient temperature. Copper (I) iodide (0.044g) was added and the reaction mixture was heated to 120°C and stirred for 22h. The reaction mixture was cooled to ambient temperature. 17% Aqueous ammonium hydroxide was added and the mixture was stirred for 1h. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with 17% aqueous ammonium hydroxide, dried (over magnesium sulphate), filtered and concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with DCM, diethyl ether, ethyl acetate and 25 methanol) to give the **title compound** (0.467g) as a beige foam-like solid.

Mass spectrum: Found: M⁺ 430

Intermediate 4

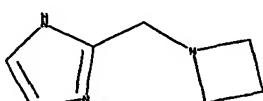


3-Amino-1-{4-[2-(1-azetidinylmethyl)-1H-imidazol-1-yl]-2-fluorophenyl}-2-pyrrolidinone

Intermediate 3 (0.467g) was dissolved in anhydrous DCM (6ml) and trifluoroacetic acid (6ml) was added. The resultant mixture was stirred at ambient temperature for 3h and then concentrated under reduced pressure. The residue was azeotroped with DCM and then purified using SPE (silica, eluting with methanol, methanol:20% aqueous ammonia) to give the title compound (0.292g) as a magnolia froth.

Mass spectrum: Found: MH^+ 330

10 Intermediate 5

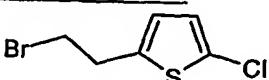


2-(1-Azetidinylmethyl)-1H-imidazole

15 To a mixture of 2-imidazolecarboxaldehyde (3.0g) and azetidine hydrochloride (3.21g) in anhydrous tetrahydrofuran (180ml) was added sodium triacetoxyborohydride (9.99g) followed by glacial acetic acid (1.72ml). The resultant mixture was stirred at room temperature for 22h, after which the insoluble material was filtered and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue purified
20 using silica SPE (eluting with DCM, methanol, methanol:20% aqueous ammonia) to give the title compound (2.63g) as a beige solid.

Gas Chromatograph Mass spectrum: Found: MH^+ 138

Intermediate 6



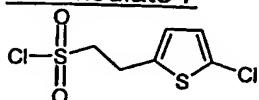
25 2-(2-Bromoethyl)-5-chlorothiophene

To a solution of 2-(5-chloro-2-thienyl)-ethanol* (12.2g) and triphenylphosphine (21.4 g) in anhydrous THF (150 ml) at 0°C was added carbon tetrabromide (27.5g). The reaction was stirred at 5°C for 15min then at room temperature for 2.5h. Ether was added and the reaction was then filtered and the filtrate concentrated. The resultant residue was purified by flash column chromatography (silica, eluting with cyclohexane:DCM 8:1) to give the title compound (15g) as an oil.

¹H NMR in CDCl_3 : 83.27 (2H, t), 3.53 (2H, t), 6.66 (1H, d), 6.76 (1H, d).

* Schick et al., J.Amer. Chem. Soc., 70, 1948, 1646.

Intermediate 7

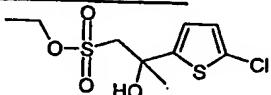


2-(5-Chloro-2-thienyl)ethanesulfonyl chloride

To a stirred solution of Intermediate 6 (14g) in acetone (125ml) was added an aqueous solution of sodium sulphite (10.5g in 125ml of water). The reaction was heated at reflux for 18h then concentrated to yield a pink solid, which was dried under vacuum at 50°C for 10 18h. A suspension of the salt in phosphorus oxychloride (90ml) was heated at 150°C for 2.5h. The reaction was concentrated and DCM and water added to the resultant residue. The organic portion was collected, concentrated and the resultant oil purified by flash column chromatography (silica, eluting with petroleum ether:toluene 7:3) to give the title compound (12.47g) as a brown oil.

15 ^1H NMR in CDCl_3 : 83.70 (2H, m), 3.22 (2H, m), 6.72 (1H, d), 6.79 (1H, d).

Intermediate 8

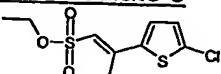


Ethyl 2-(5-chloro-2-thienyl)-2-hydroxy-1-propanesulfonate

20 A solution of ethyl methanesulphonate (4.97g) in THF (20ml) was added dropwise to a solution of lithium hexamethyldisilylamide (42.0 ml of 1M solution in THF plus 20ml of THF) at -78°C under nitrogen, and the solution was stirred for 30min. A solution of 2-acetyl-5-chlorothiophene (6.75g) in THF (70ml) was added to this over 15min and the temperature maintained at -78°C for 90min. The reaction was quenched with saturated aqueous ammonium chloride and the mixture extracted with ethyl acetate. The combined organic fractions were washed with brine; dried (over magnesium sulphate) and concentrated under reduced pressure to afford a crude oil that was purified by Biotage™ chromatography (silica, eluting with ether-cyclohexane 1:3) to give the title compound (10.9g) as a colourless oil.

25 ^1H NMR (CDCl_3): 86.79(1H, d), 6.73(1H, d), 4.26(2H, m), 4.14(1H, s), 3.32(1H, d), 3.52(1H, d), 1.8(3H, s), 1.36(3H, t).

Intermediate 9



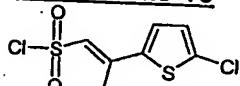
35 Ethyl (1E)-2-(5-chloro-2-thienyl)-1-propene-1-sulfonate

A solution of Intermediate 8 (10.9g) in DCM (300 ml) was cooled to 0°C under nitrogen, to which was added methanesulphonic acid (15.0ml) in a dropwise fashion. After stirring for 90min, saturated aqueous sodium bicarbonate was added, followed by water and brine. The layers were separated and the aqueous layer back extracted with DCM; the organic

5 fractions were combined, washed with brine and dried (over magnesium sulphate) and concentrated under reduced pressure. The crude mixture was purified using Biotage™ chromatography (silica, eluting chloroform and 15% *tert*-butylmethyl ether in cyclohexane) to give the title compound (2.9g) as a white crystalline solid.

10 ^1H NMR (CDCl₃): δ 7.16(1H, d), 6.92(1H, d), 6.47(1H, d) 4.26(2H, q), 2.50(3H, d), 1.42

Intermediate 10



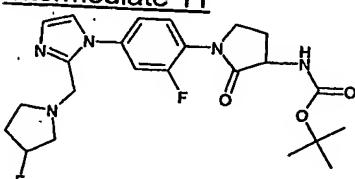
(1E)-2-(5-Chloro-2-thienyl)-1-propene-1-sulfonyl chloride

15 Tetrabutylammonium iodide (4.03g) was added to a solution of Intermediate 9 (2.9g) in acetone (180ml) under nitrogen and the solution heated under reflux for 17h. The solution was cooled and concentrated under reduced pressure to produce a yellow-brown solid. This was stirred in phosphorus oxychloride (30ml) at room temperature for 3.5h, after

20 which the volatiles were removed under reduced pressure and the residue co-evaporated twice with toluene. The residue was purified using Biotage™ chromatography (silica, eluting with, cyclohexane and cyclohexane:diethyl ether 1:1) to give the title compound (2.1g) as a yellow crystalline solid.

^1H NMR (CDCl₃): δ 7.31(1H, d), 6.99(1H, d), 6.96(1H, q), 2.64(3H, d).

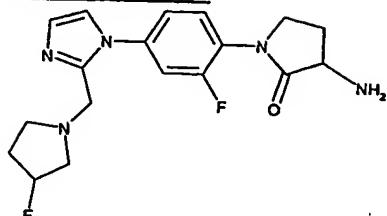
25 Intermediate 11



1,1-Dimethylethyl [1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1H-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]carbamate,

30 The title compound was prepared from Intermediate 2 and Intermediate 13 using the synthetic procedure described for Intermediate 3.

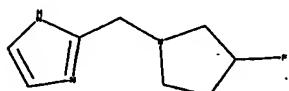
Mass spectrum: Found: MH⁺ 462
H.p.l.c. Rt 2.19min

Intermediate 123-Amino-1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1H-imidazol-1-yl}phenyl)-2-pyrrolidinone

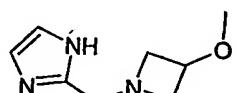
5 The title compound was prepared from Intermediate 11 by treatment with hydrogen chloride in methanol using the synthetic procedure described for Intermediate 4. Mass spectrum: Found: MH^+ 362

Intermediate 13

10

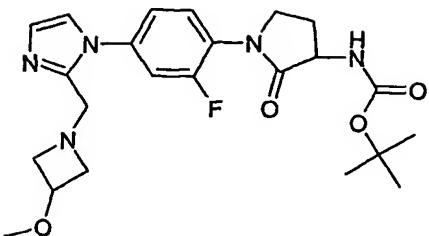
2-[(3-Fluoro-1-pyrrolidinyl)methyl]-1H-imidazole

The title compound was prepared from 2-imidazolecarboxaldehyde and 3-fluoropyrrolidine 15 hydrochloride using the synthetic procedure described for Intermediate 5. Gas Chromatography Mass spectrum: Found: MH^+ 170 Intermediate 14

2-[(3-Methoxy-1-azetidinyl)methyl]-1H-imidazole (GSK222768A)

20 The title compound was prepared from 2-imidazolecarboxaldehyde and 3-methoxyazetidine hydrochloride using the synthetic procedure described for Intermediate 5. Gas Chromatograph Mass Spectrum: Found: MH^+ 168

25 Intermediate 15

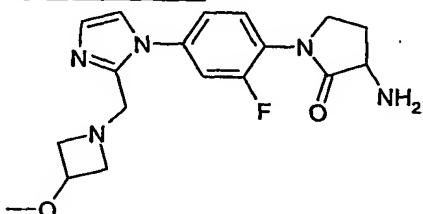


1,1-Dimethylethyl {1-[2-fluoro-4-(2-{3-(methyloxy)-1-azetidinyl}methyl]-1H-imidazol-1-yl)phenyl}-2-oxo-3-pyrrolidinyl carbamate (GSK243789A)

The title compound was prepared from Intermediate 2 and Intermediate 14 using the synthetic procedure described for Intermediate 3.

Mass spectrum: Found: MH^+ 460

Intermediate 16



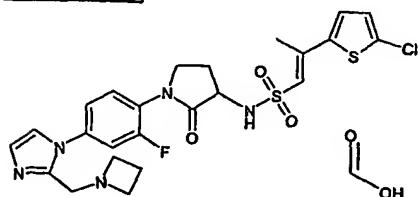
10 3-Amino-1-[2-fluoro-4-(2-{3-(methyloxy)-1-azetidinyl}methyl)-1H-imidazol-1-yl)phenyl]-2-pyrrolidinone (GSK243791A)

The title compound was prepared from Intermediate 15 using the synthetic procedure described for Intermediate 4.

Mass spectrum: Found: MH^+ 360

15

Example 1



20 (1E)-N-(1-{4-[2-(1-Azetidinylmethyl)-1H-imidazol-1-yl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-2-(5-chloro-2-thienyl)-1-propene-1-sulfonamide formate (i.e. Formic acid (1E)-N-(1-{4-[2-(1-azetidinylmethyl)-1H-imidazol-1-yl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-2-(5-chloro-2-thienyl)-1-propene-1-sulfonamide (1:1))

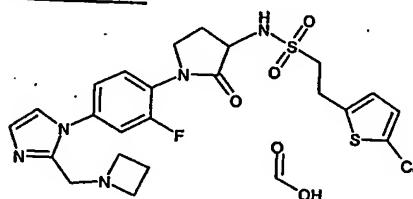
Intermediate 4 (0.046g) was dissolved in anhydrous acetonitrile (1.5ml) at room temperature. To this solution was added pyridine (0.1ml) and Intermediate 10 (0.036g).

The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The resultant residue was purified by mass directed preparative h.p.l.c. to give the title compound (0.006g) as a cream solid.
 Mass spectrum: Found: MH^+ 550

5 H.p.l.c. Rt 2.47min

1H NMR (MeOD): δ 2.18 (2H, m), 2.28 (2H, m), 2.49 (3H, s), 2.66 (1H, m), 3.76 (4H, m), 3.89 (1H, m), 4.07 (2H, s), 4.46 (1H, t), 6.98 (1H, s), 6.98 (1H, d), 7.11 (1H, s), 7.28 (1H, d), 7.37 (1H, s), 7.41 (1H, d), 7.57 (1H, d), 7.66 (1H, t), 8.41 (1H, s)

10 Example 2



N -(1-[4-[2-(1-Azetidinylmethyl)-1H-imidazol-1-yl]-2-fluorophenyl]-2-oxo-3-pyrrolidinyl)-2-(5-chloro-2-thienyl)ethanesulfonamide formate

The title compound was prepared from Intermediate 4 and Intermediate 7 using the 15 synthetic procedure described for Example 1.

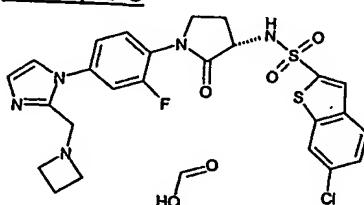
Mass spectrum: Found: MH^+ 538

H.p.l.c. Rt 2.43min

1H NMR (MeOD): δ 2.19 (2H, m), 2.33 (2H, m), 2.66 (1H, m), 3.67-3.70 (4H, m), 3.79 (1H, t), 3.85-3.95 (4H, m), 4.18 (2H, s), 4.50 (1H, t), 6.78 (2H, s), 7.12 (1H, s), 7.39 (1H, s),

20 7.41 (1H, d), 7.56 (1H, d), 7.68 (1H, t), 8.38 (1H, s)

Example 3

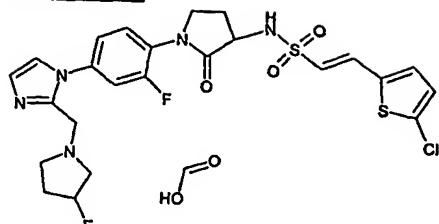


N -((3S)-1-[4-[2-(1-Azetidinylmethyl)-1H-imidazol-1-yl]-2-fluorophenyl]-2-oxo-3-pyrrolidinyl)-6-chloro-1-benzothiophene-2-sulfonamide formate

The title compound was prepared from Intermediate 4 and 6-chloro-1-benzothiophene-2-sulfonyl chloride using the synthetic procedure described for Example 1.

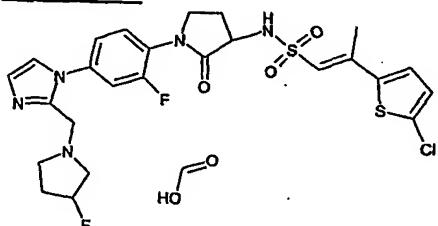
Mass spectrum: Found: MH^+ 560

H.p.l.c. Rt 2.53min

Example 4

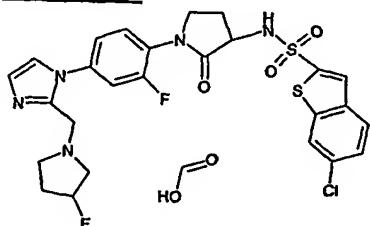
(E)-2-(5-Chloro-2-thienyl)-N-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1H-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]ethenesulfonamide formate

5 The title compound was prepared from Intermediate 12 and (E)-2-(5-chloro-2-thienyl)ethenesulfonyl chloride using the synthetic procedure described for Example 1.
 Mass spectrum: Found: MH^+ 568
 H.p.l.c. Rt 2.57min

10 Example 5

(1E)-2-(5-Chloro-2-thienyl)-N-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1H-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]-1-propene-1-sulfonamide formate

15 The title compound was prepared from Intermediate 12 and Intermediate 10 using the synthetic procedure described for Example 1.
 Mass spectrum: Found: MH^+ 582
 H.p.l.c. Rt 2.56min

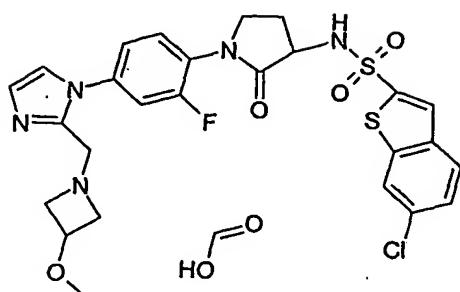
Example 6

20 6-Chloro-N-[1-(2-fluoro-4-{2-[(3-fluoro-1-pyrrolidinyl)methyl]-1H-imidazol-1-yl}phenyl)-2-oxo-3-pyrrolidinyl]-1-benzothiophene-2-sulfonamide formate

The title compound was prepared from Intermediate 12 and 6-chloro-1-benzothiophene-2-sulfonyl chloride using the synthetic procedure described for Example 1.
 25 Mass spectrum: Found: MH^+ 592

H.p.l.c. Rt 2.64min

Example 7



5 6-Chloro-N-{1-[2-fluoro-4-(2-{[3-(methyloxy)-1-azetidinyl]methyl}-1H-imidazol-1-yl)phenyl]-2-oxo-3-pyrrolidinyl}-1-benzothiophene-2-sulfonamide formate
 The title compound was prepared from Intermediate 16 and 6-chloro-1-benzothiophene-2-sulfonyl chloride using the synthetic procedure described for Example 1.
 Mass spectrum: Found: MH^+ 590

10 H.p.l.c. Rt 2.58min

In vitro assay for inhibition of Factor Xa

Compounds of the present invention were tested for their Factor Xa inhibitory activity as determined *in vitro* by their ability to inhibit human Factor Xa in a fluorogenic assay, using

15 Rhodamine 110, bis-CBZ-glycylglycyl-L-arginine amide as the fluorogenic substrate. Compounds were diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM Tris-HCl, 150mM NaCl, 5mM CaCl₂, pH 7.4. containing human Factor Xa (final conc. Of 0.0003U.ml-1). Compound and enzyme were preincubated for 15min prior to

20 addition of the substrate (final conc. of 10 μ M). The reaction was stopped after 3 hrs with the addition of H-D-Phe-Pro-Arg-Chloromethylketone. An L JL-Analyst fluorimeter was used to monitor fluorescence with 485 nm excitation/535 nm emission. To obtain IC₅₀ values the data were analysed using ActivityBase® and XLfit®.

25 Calculation of Ki values:

$$Ki = IC_{50}/(1 + [Substrate]/Km)$$

The Ki value for the above assay can be obtained by dividing the IC₅₀ value by 1.6.

All of the synthetic Example compounds were tested by the above described *in vitro* assay

30 and were found to exhibit Factor Xa inhibitory activity. Preferably compounds have a Ki value of less than 1 μ M (Examples 1, 2, 3, 4, 5, 6, 7). More preferably, compounds have a

Ki value of less than 100nM (Examples 1, 2, 3, 4, 5, 6, 7). Most preferably, compounds have a Ki value of less than 10nM (Examples 1, 2, 5, 6, 7).

Method for measurement of Prothrombin Time (PT)

5

Prothrombin time of compounds according to the invention may be determined using the following assay.

10 Blood is collected into a sodium citrate solution (ratio 9:1) to give a final concentration of 0.38% citrate. Plasma is generated by centrifugation of citrated blood samples at 1200 x g for 20 min at 4°C and stored at -20°C until use. PT analysis is conducted using plasma pooled from 4 separate donors (2 male and 2 female).

15 The PT test is performed using the BCS Coagulation Analyzer (Dade Behring). For assay, 50 ul of plasma containing test compound at concentrations ranging from 0.03 to 100 uM (made from a 100 uM stock containing 1% DMSO in plasma) is combined with 100 ul of Thromboplastin C Plus (Dade Behring). Upon addition of the reagents, absorbance at 405 nm is monitored and time to clot formation is determined (normal range for human plasma is 10.6-12.4 seconds).

20

General purification and analytical methods

LC/MS Method

25 Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3μm, 3.3cm x 4.6mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 95% acetonitrile and 0.05% HCO₂H in water (solvent B), using the following elution gradient 0-0.7 minutes 0% B, 0.7-4.2 minutes 0→100% B, 4.2-5.3 minutes 100% B, 5.3-5.5 minutes 100→0% B at a flow rate of 3 ml/minutes (System 1). The mass spectra (MS) were recorded on a Fisons VG Platform mass spectrometer using electrospray positive ionisation [(ES+ve to give MH⁺ and M(NH₄)⁺ molecular ions] or electrospray negative ionisation [(ES-ve to give (M-H)⁻ molecular ion] modes.

30 ¹H nmr spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard.

35

Biotage™ chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil.

Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cm x 10mm i.d.) with 0.1% HCO₂H in water and 95% MeCN, 5% water (0.5% HCO₂H) utilising the following gradient elution conditions: 0-1.0 minutes 5%B, 1.0-8.0 minutes 5→30%B, 8.0-8.9 5 minutes 30%B, 8.9-9.0 minutes 30→95%B, 9.0-9.9 minutes 95%B, 9.9-10 minutes 95→0%B at a flow rate of 8ml minutes⁻¹ (System 2). The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent 10 Technology Ltd.

GC/MS Method.

Analytical GCMS was conducted on a Micromass GCT with CTC Combipal injector using a 5% Phenylmethyl siloxane column (30m x 0.25mm x 0.25µm). A temperature ramp of 15 80°C to 320°C at 50°/min was used (run time 10 min), with a gas flow of helium at 1.5ml/min (split injection 1:100) and methane as the collision gas.